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Chapter 5

Social cognition in addiction

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Abstract

Social problems and the neglect of social relationships and activities are essential features of substance use disorders (SUD). Recently, social impairments of individuals with specific SUD have begun to be characterised at the cognitive, emotional, and behavioural level by neuropsychological and social neuroscience methods. Growing evidence suggests that specific SUD are associated with specific dysfunctions in social cognition and interaction and that these impairments likely contribute to the social dysfunctions occurring in the daily life of SUD-affected people. It has also been proposed that socio-cognitive deficits – such as decreased emotional empathy, worsened mental perspective-taking, and a blunted ability to perceive reward from social interactions – play a prominent role in the establishment, development, and course of therapeutic relationships, where they potentially hamper treatment success. The present chapter provides a brief overview of the current status of social cognition research in SUD and discusses future directions for the assessment and treatment of social impairments in SUD.

Keywords: addiction, substance use disorder, alcohol, cannabis, stimulants, altruism, fairness, joint-attention, moral decision-making, mirror neurons, social reasoning, emotion perception, emotion recognition, empathy, social interaction, neuroeconomics, game theory.

Introduction

Humans have developed specific cognitive functions in order to understand themselves and others, to predict and affect the behaviour of others, and to dynamically interact with their social environment (1-3). These higher cognitive functions have been congregated under the umbrella term *social cognition*. This broad array of functions includes more perceptive abilities, such as emotion perception and recognition, self-awareness and self-perception, emotional empathy, and mental and emotional perspective-taking also called *Theory-of-Mind* (ToM), as well as interactive social functions, such as social gaze contact, social decision-making, and the ability to perceive reward from social contacts, and, finally, social attitudes and values, such as altruism, fairness, trust, morale, stereotypes, and prejudices (1-4). Unsurprisingly, given that social functioning in daily life depends on intact social cognition, disturbances in these functions have been shown to be crucial factors in the development, progress, and prognosis of psychiatric conditions such as schizophrenia (5,6) and depression (7). Analogously, it has been proposed that dysfunctional social cognition and interaction likewise play a key role in the origin and course of substance use disorders (SUD) (8-10). It has also been suggested that chronic drug use, e.g., of stimulants, impacts the fronto-striatal reward system by enhancing the value of the substance, while simultaneously reducing sensitivity to the rewards obtained via social activities (11,12). Accordingly, drug-induced changes in brain regions and neurotransmitter systems involved in social cognition, social interaction, and social reward processing are assumed to contribute to a further decrease in social contacts and social support, leading to an increase in social isolation, aggression, and depressive symptoms (10,13). This coincides with a further reduction in social reward resources, ongoing social withdrawal, and the establishment of the drug as the main source of reward, resulting in maintained substance use and recurrent relapses (10) (see **Figure 1**). Taken together, drug-related changes in social reward and social cognition likely contribute to the social problems and the decay of social relationships in individuals with SUD. Therefore, it is also likely that disturbances in social perception and behaviour strongly compromise therapeutic relationships, and, thus, hamper the success of any addiction treatment. Consequently, interpersonal problems related to social cognition deficits likely contribute to high relapse rates found across a range of SUD. Importantly, social cognitive deficits can recover partially simply through drug abstinence, e.g., as shown for cocaine users (14) and alcohol dependence (AD) (15), and several treatment approaches have been demonstrated to have a normalising effect on social cognitive abilities e.g., in major depression (7), which encourages the inclusion of available social training techniques and development of social competences and social reward in psychotherapy of SUD. However, specific treatment modules focussing on the rehabilitation of social cognition and reward are so far lacking for SUD, even though they might have a positive impact on the overall treatment success.

At the beginning of this chapter, brief definitions of the most important socio-cognitive functions will be given. Thereafter, investigations characterizing, quantifying, and explaining disturbances of

different socially-related mental functions will be reviewed with respect to specific SUD. Overall, only performance measures and measures of behaviour will be discussed in this chapter, while questionnaire-based research will be omitted in order to keep the focus on cognitive processes. Moreover, although empathogens such as 3,4-methylenedioxymethamphetamine (MDMA) have a very low addictive potential, they (i) play a role in addiction medicine primarily as a frequently co-used substance class and (ii) have – per definition – a strong effect on social cognition and thus they will be discussed below, alongside addiction-related substances.

Definitions of socio-cognitive functions and their measurement

Emotion recognition, also called ***cognitive empathy***, ***affect recognition***, or ***emotion perception***, is the capability to recognise and understand the emotions of others from faces, voices, gestures, and situational contexts (16). Numerous studies with drug users have employed emotional facial expression tasks, primarily based on the famous picture set of Ekman and Friesen (17). Beyond simple static face stimuli with different intensities of emotion expression, presentations of dynamic emotion expressions using short movies or morphed Ekman faces have also been developed (e.g., 18,19). The *Comprehensive Affect Test System* (CATS-A), includes emotion recognition from Ekman faces and from voices, as well as the ability to align the emotional load of faces and voices (20). The *Multifaceted Empathy Task* (MET) also deserves mention as an example of the assessment of cognitive empathy using complex, emotionally-laden scenes (21).

Emotional empathy is defined as a person's emotional response to another person's emotional state, i.e., the ability to feel what another person feels (22). Beyond basic cognitive empathy, emotional empathy can also be measured, e.g., with the MET (21).

Mental and ***emotional perspective-taking***, also called ***mentalizing*** or ***ToM***, reflects the ability "*to propositionally reason from one's theory of how minds operate and how social situations affect mental states in general, in order to represent the mental state of a particular individual given a particular situation*" (3, p. 263). A famous emotion recognition task – although perhaps more commonly interpreted as a ToM-Task – the *Reading the Mind in the Eyes Task* (RMET), in which emotional states have to be inferred only from eye pairs, has been applied frequently in drug using populations (23). In addition, tests measuring the ability to detect social *faux pas*' (24) and to understand humour (25,26) have been used to measure aspects of perspective-taking and ToM. A final example – and one with high ecological validity – is the video-based *Movie for the Assessment of Social Cognition* (MASC), which assesses the understanding of emotions, thoughts and intentions, and concepts such as false belief, *faux pas*, metaphor, and sarcasm in everyday-life situations (27).

Social decision-making describes the ability to process multiple alternatives and to choose an optimal course of action in a social environment, which is usually operationalised using socially interactive

tasks derived from game theory (28). A variety of such social decision-making games is discussed elsewhere (29,30).

Moral decision-making or ***moral judgement*** is a complex cognitive process enabling individuals to judge actions of other individuals on the basis of habits, values, and norms orienting the conduct in a certain social group (31). This kind of behaviour is usually operationalised by presenting hypothetical moral dilemmas – often with varying levels of personal involvement – and asking for preferred choices (32). A great variety of text- and picture-based vignettes with hypothetical dilemmas have been developed, such as the well-known examples of Greene et al (33) and Koenigs et al (34), but also newer stimulus sets (35). Moreover, vignettes specifically related to addiction have also been used (36). Recently, a normative moral video database – the Moral and Affective Film Set (MAAFS) – has also been proposed (37).

Social reward can be defined as perceiving pleasure during social interactions or social commitment. Of note, reward by non-social objects, such as money, gifts, and drugs of abuse, as well as social reward, all activate the same reward-related networks in the brain (38,39). So far, experimental tasks usually applied in social neuroscience contexts have been developed to measure facets of social reward such as positive social feedback (40), initiated joint attention (41), or charitable decision-making (42).

Studies on social cognition and interaction in substance use disorders

Alcohol

Emotion recognition and cognitive empathy

Since the end of the 1980s, emotion recognition from faces has been investigated in individuals with AD across dozens of studies. Most of these identified either emotion-specific or global impairments, or both, in the decoding of emotions from faces (15,43-54). However, there are also several studies that were not able to identify impaired performance in facial emotion recognition tasks in similar patient groups (53,55-58). Moreover, there are contradicting results regarding the impact of abstinence: While the first longitudinal study showed no improvement of impaired emotional face recognition after 3 months of abstinence (49), a recent study showed almost complete recovery of such deficits in the same time period (15). Two cross-sectional studies reported sustained emotion recognition impairments in mid-term abstinent (>2 months) AD individuals (50,52), whereas another cross-sectional study did not detect accuracy changes in a face recognition task in patients with very long abstinence periods (>12 months, mean 75 months) (59). However, the latter study showed slower early processing of emotional facial stimuli in long-term abstinent AD patients using an electrophysiological Event Related Potentials paradigm (59). Finally, a recent meta-analysis including only 12 of the previous studies confirmed global face recognition deficits of moderate effect size (total

score Cohen's d=0.65), while also demonstrating that the strongest deficits are for the recognition of disgust (d=0.62) and anger (d=0.47) and the weakest for happiness (d=0.19) (60).

In addition to face recognition deficits, worse emotion recognition from voices (prosody) has been shown repeatedly in AD patients (57,61,62). Given that deficits in emotion recognition from body postures and music have also been reported, it has therefore been suggested that AD individuals suffer from a generalized emotional decoding impairment (54,62). In line with findings showing face and prosody recognition deficits in AD patients, emotion recognition (cognitive empathy) from complex emotionally-laden scenes, as presented in the MET, was also recently demonstrated to be diminished (63). Furthermore, a number of studies have indicated that the integrated processing of face and voice recognition in cross-modal conditions is specifically affected in AD patients (43,53,64). Patients with AD not only fail in the categorisation of emotions from faces or voices, but also generally overestimate the intensity of emotional expressions (48), have a globally increased identification threshold for emotions (46), or misidentify emotions (65). It has been shown that episodic memory and cognitive flexibility are strongly associated with emotional face recognition, suggesting that socio-cognitive deficits might be partially explained by more basal cognitive impairments (45). However, another study demonstrated that visuo-motor impairment cannot completely explain face recognition deficits in AD (47). In addition, face recognition abilities in AD patients have been shown to be modulated by gender (43) and are related to self-reported interpersonal problems (51). As several studies have found that emotion recognition performance is correlated with severity markers of chronic alcohol use, such as binge drinking, early onset of use, drinks consumed in the last 3 months and number of detoxifications, it has been suggested that such deficits may be acquired more than they are signs of a predisposition (43,44,61,65,66).

A structural imaging study found that AD individuals displayed reduced grey matter volume in the inferior frontal cortex (IFC) and insula. IFC grey matter volume was correlated with number of detoxifications and with the recognition of fearful faces (67). A combined structural and functional imaging (fMRI) study revealed that patients with AD displayed decreased activation in response to aversive faces in bilateral fusiform gyrus (FG), right middle frontal gyrus, right inferior parietal lobule and left cerebellum, which were largely explained by grey matter differences. Moreover, because an increased activation of the anterior cingulate cortex (ACC) was correlated with less previous lifetime alcohol intake, longer abstinence periods, and less subsequent binge drinking, the authors concluded that chronic alcohol use appears to impair treatment outcome via exerting neurotoxic effects on the ACC (68). Schuckit et al (69) showed that baseline fMRI activation patterns, specifically in insular and frontal regions, predicted heavy drinking and alcohol problems in AD five years later. Importantly, only poorer emotion recognition performance (but not emotional-perspective-taking and affective responsiveness) at baseline was able to predict treatment outcomes of AD, such as relapse or dropout (70).

Taken together, these findings suggest that patients with AD display difficulties in the recognition and integration of emotions from faces, voices, and other sources. These deficits might be partially induced by neurotoxic effects of chronic alcohol intake, but they may also be useful for the prediction of treatment success.

Emotional empathy

In an emotional contagion task using emotional facial expressions, AD patients reported fewer positive and more negative emotions when confronted with respectively valent face stimuli than controls, indicating emotional empathy to be lower for positive emotions, but increased for negative. In addition, the mimicry of angry faces, as assessed by filming the participants while they were watching the stimuli (71), was more pronounced in Type-II AD patients (according to Cloninger subtypes of alcoholism, 72) than Type-I patients and controls (71). In contrast, emotional empathy was not altered in AD individuals in a study applying the MET, although their cognitive empathy was impaired (63).

Perspective-taking and ToM

The most commonly used ToM task – the RMET – has been applied in seven published studies, of which four found a significant deficiency in "mind reading" in individuals with AD (73-76), while three did not report any group differences (77-79). A recent meta-analysis that included all of these studies – with the exception of the newest one (79) – plus an unpublished doctoral thesis, came to the conclusion of a significant deficit in RMET performance with a moderate effect size (Cohen's d=0.46) existing in patients with AD (60).

An fMRI study additionally reported that a diagnosis of AD was associated with decreased activity of the right anterior insular cortex while performing the RMET (73). The second most commonly used ToM task is the *Faux pas test*: two studies have found impaired performance on this task in AD (75,80), while one has not (81). Deficits in the understanding of irony and humor have also been reported for AD individuals in three independent studies (26,58,81), although one further study did not detect changes in the *Strange Stories* test assessing the comprehension of metaphors and irony (82). Furthermore, two video-based paradigms for the assessment of ToM and mental perspective taking have revealed a deficit in the affective component of ToM, while its cognitive component was preserved (76,83). AD individuals were also shown to display deficits in *False Belief* tasks (specifically in the tracking of others beliefs) (84) and in social problem solving, both of which depend on the ability to infer mental states of others (85). Two meta-analyses so far have assessed the effect sizes across several ToM paradigms and both concluded that ToM abilities are impaired in AD individuals: The first of these included 8 studies with 187 patients and 187 controls and found a very strong effect size (Hedges' g=1.62) (86). The second one included 12 studies with 317 patients and 298 controls and reported a moderate effect size (d=0.58) (60).

Importantly, ToM deficits in AD have been shown to be correlated with executive and memory functions as well as with depressive symptoms (26,75,76), and to increase with the duration of AD (73,80). Taken together, a number of studies have shown impairments in ToM and perspective-taking abilities that might be induced or at least partially caused by chronic alcohol intake. Moreover, these disturbed abilities might be linked to other cognitive or emotional impairments and may not be changes specific to mentalizing.

Social decision-making

AD individuals have been consistently reported to reject unfair offers in the Ultimatum Game more often than healthy controls (87-89). The proportion of rejected unfair offers has been shown to be correlated with elevated physiological arousal as assessed by the skin conductance response (89) as well as with reward impulsivity measured using a delay discounting task (87). These findings indicate that AD individuals have a higher sensitivity to unfairness, or that they have more problems with controlling their emotions in unfair situations, resulting in more aggressive or retributive responses (87-89).

Moral decision-making

Two studies have demonstrated that patients with AD endorse utilitarian choices significantly more than controls (90,91). Another study also observed – although below the margin to be reported as statistically significant – elevated utilitarian choices in individuals with AD (92). Moreover, in a group of polysubstance users, severity of alcohol use specifically predicted the proportion of utilitarian judgments (93). Notably, moral judgement was changed in spite of individuals having sufficient knowledge of explicit social and moral norms and normal responses to non-moral or impersonal moral dilemmas (90). Moreover, neither non-social decision-making, measured with the Iowa Gambling Task, nor trait impulsivity and mood predicted moral judgements (91,92). However, poorer decoding of fear and disgust from faces was correlated with more utilitarian choices (91) and AD individuals did not show aversive psychophysiological responses (heart rate) to personal moral violations (94). To summarize, AD seems to be associated with changes in moral judgment and, specifically, it may be that alcohol-induced damage to the ventromedial prefrontal cortex (VMPFC) causes emotional dysfunction, leading to a more utilitarian approach to moral judgment (90).

Cannabis

Emotion recognition and cognitive empathy

Several studies have investigated emotion recognition from faces in moderate, heavy, and dependent cannabis users and all reported a generalized deficit in this kind of emotion processing (95-98). This effect was found in current (95,96,98) and medium-term abstinent users (mean 3.2 months) (97), thus the deficits are likely not fully explained by acute and postacute detrimental effects of Δ-9-

tetrahydrocannabinol (THC) on emotion recognition (99). Importantly, higher levels of schizoptypy in cannabis users also failed to explain the results in one of the studies (96) and deficits might be more pronounced in the recognition of negative emotions (97). Interestingly, in a well-powered fMRI investigation it was demonstrated that adolescent cannabis users showed a stronger activation of the bilateral amygdala in response to angry faces, while their cortical areas did not discriminate angry vs. neutral faces, unlike in controls (100). The authors concluded that early cannabis use might be associated with hypersensitivity to signals of threat, perhaps placing users at risk for mood disorders in adulthood. Moreover, enhanced recognition of angry faces (101), as well as misattribution of sad faces (102), has been shown to predict later initiation cannabis use in adolescents. In sum, these findings all point to emotion recognition problems in cannabis users that might be partially present before onset of use and worsened further by acute, postacute, and chronic cannabis effects.

Emotional empathy

Unpublished pilot data from our lab suggest that at least moderate use of cannabis (mean 2.8g/week) was not associated with changes in cognitive and emotional empathy in the MET in a modest-powered sample of 21 users vs. 21 healthy controls (103). Published data on emotional empathy measured with a behavioural task in cannabis users are not available yet. However, an early interview-based study showed that smoking cannabis acutely decreased affective resonance between the cannabis-intoxicated individuals and their non-intoxicated interaction partners (104).

Perspective-taking and ToM

Perspective-taking abilities seem to be largely intact in chronic cannabis users when measured with the RMET (95,103), a cartoon-based fMRI task (105), and the MASC (103). Moreover, when assessed using the *Eyes and Hinting Test*, cannabis use was not related to ToM performance in schizophrenia patients (106). However, a small fMRI study found some differences in brain activations (but no performance differences) between chronic cannabis users (n=15) and controls (n=14) while watching cartoon stories in which the characters show various facets of cooperative behaviour (105).

Social decision-making

Studies investigating social behaviour with game-theoretical approaches in cannabis users have not yet been published. In our small pilot study in the context of a master thesis, we found no significant differences in prosocial behaviour between modest chronic cannabis users and matched controls in three neuroeconomic games – the *Promise Task*, the *Distribution Game*, and the *Dictator Game*. Nevertheless, there was a statistical trend (p=.052) for cannabis users to share more money than controls did with the opposite player in the *Dictator Game*, indicating rather prosocial fairness preferences (103).

Social reward

Employing a novel interpersonal pleasant touch fMRI paradigm to dependent, but recently abstinent, male cannabis users and healthy controls, Zimmermann et al (107) found that, relative to the controls, cannabis users reported lower reward responsiveness to female touch, as well as decoupling of striatal activations and subjectively reported reward experiences. However, neural processing of pleasant touch in general was seemingly unchanged in dependent cannabis users (107).

Stimulants

Emotion recognition and cognitive empathy

Most studies with cocaine and methamphetamine users have revealed that their ability to identify basic facial affect expressions is largely unimpaired (108-114). However, a few studies have found specific alterations in fear (115-118) and anger processing (115) from faces in regular users of cocaine or methamphetamine. Moreover, in polysubstance users, fear and anger recognition performance was negatively correlated with cocaine use intensity (119), while another study did not show an effect of stimulant polysubstance use on facets of cognitive empathy when assessed with complex stimuli (120). Using a facial affect matching task, a fMRI study in methamphetamine users also did not detect task-related changes, but rather different cortical activation patterns in regions relevant for social cognition (114). Non-medical users of methylphenidate without attention-deficit/hyperactivity disorder (ADHD), who have taken the drug for neuroenhancement purposes, exhibited problems with cognitive empathy for complex emotional scenes measured with the MET (121). Interestingly, cocaine users with a comorbid ADHD diagnosis also showed impaired cognitive empathy in the MET (122). One investigation has shown that chronic cocaine users displayed problems in emotion recognition from voices (prosody) as well as in the detection of matches and mismatches between emotional faces and voices when both were presented together (108). Differences in study sample characteristics may account for some of the discrepant results discussed above, given that most of the studies had relatively small sample sizes and often included stimulant-preferring polysubstance users with further psychiatric comorbidities. Accordingly, Ersche et al. demonstrated that fear and anger recognition deficits in cocaine users were mainly explained by lower IQ and concurrent opioid dependence, respectively (115), while an additional impact of ADHD on cognitive empathy has recently been shown (122). Of note, well-powered studies did not find alterations in visual emotional processing, but rather deficient prosodic emotion recognition, in relatively pure recreational and dependent cocaine users with a low burden of psychiatric comorbidities (108,123).

Emotional empathy

In the Zurich Cocaine Cognition Study ($ZuCo^2St$), recreational and dependent cocaine users (123) as well as stimulant polysubstance users (120) reported lower emotional empathy ratings to the

photorealistic affective stimuli in the MET. In cocaine users, implicit emotional empathy was correlated specifically with weekly and lifetime cocaine dose and emotional empathy deficits were generally most pronounced in early age-of-onset users (123). Interestingly, comorbid ADHD had an additional impact on emotional empathy but did not explain the empathy impairment in general (123). In a longitudinal analysis of the ZuCo^{2}St sample it was shown that emotional empathy can recover when cocaine use is reduced or ceased (14).

A fMRI study has shown that methamphetamine users showed reduced emotional empathy in a cartoon-based task, which was accompanied by lower activation of the orbitofrontal cortex (OFC), both temporal poles, and the right hippocampus, relative to healthy controls (124). Finally, neuroenhancement methylphenidate users taking relatively low doses did not exhibit abnormalities in emotional empathy (121).

Perspective-taking and ToM

Dependent, but not recreational, cocaine users committed more errors in the video-based MASC, suggesting that worse mental perspective-taking is associated with cocaine addiction, yet not recreational use, or related premorbid characteristics (123). Additionally, moderate correlations between task performance and several subjective and objective cocaine intake indices have been found (123). Importantly, a concurrent ADHD diagnosis had a modulating impact on perspective-taking, i.e., only severe users with a comorbid ADHD symptomatology showed significant impairments (122,123). Studies using the RMET demonstrated that methamphetamine (118,125) but not cocaine users (116,123) displayed alterations of "mind reading" from eye pairs. A single study in methamphetamine users, investigating perspective-taking with a story-based task, found only a trend for impaired ToM abilities in the drug users (118). A trend for weaker perspective-taking abilities has also been reported for non-medical methylphenidate users (121).

Social decision-making

In the ZuCo^{2}St, recreational and dependent cocaine users showed reduced prosocial decisions in comparison to a control group in two social interaction tasks, given that cocaine users preferred higher monetary payoffs for themselves and cared primarily about efficiency and less about fairness (126). As no correlation between fairness preferences and cocaine use intensity was found, the authors proposed that self-serving behaviour might represent a predisposition for stimulant use (126); however, in a longitudinal analysis of these data the reduction in cocaine use was weakly associated with improved social decision-making, indicating that these deficits might be at least partially drug-induced (14). Interestingly, it was also reported that methylphenidate neuroenhancement users display altered social decision-making (121).

Verdejo-Garcia et al (111) investigated social decision-making during fMRI in cocaine-dependent individuals with and without a comorbid personality disorder. The acceptance rate for fair and unfair

offers was not affected in cocaine users. However, compared to controls, cocaine users displayed reduced activation in the dorsolateral prefrontal cortex during evaluation of unfair offers and reduced activation in the subgenual ACC and the midbrain during rejection of these offers. Additionally, cocaine users showed increased activation in superior frontal and lateral OFC regions during the evaluation of unfair offers, which was correlated with deficient facial affect recognition (111).

Moral decision-making

A fMRI study did not find differences in the behavioural responses to moral dilemmas between cocaine-dependent patients and healthy controls, although the patients displayed decreased activation of the ACC, left insula and brain stem as well as reduced functional connectivity between ACC, thalamus, insula, and brain stem (127). Recently, it was additionally shown that cocaine-using incarcerated individuals displayed impaired picture discrimination in the ventral ACC, VMPFC, lateral OFC, and left ventral striatum compared to non-cocaine-using incarcerated individuals when identifying pictures that did or did not depict immoral actions (128).

Social reward

In an interactive social gaze paradigm, cocaine users showed blunted emotional responses and less activation of the VMPFC during social gaze interaction, supporting the assumption that social eye-contact might be less rewarding for them (12). Importantly, the activation of the VMPFC was correlated with the size of the social network of the cocaine users, indicating that a blunted ability to perceive this implicit form of social reward is reflected in diminished real-life social functioning (12). In another complex fMRI experiment, cocaine users also displayed a reduced reward signal in the VMPFC in the context of positive social feedback. The social reward-related activation in the VMPFC overlapped with a reduced response to object reward, which was additionally correlated with years of cocaine use (11). As the VMPFC has been proposed to be critically involved in the encoding and maintenance of reward value (129), it was proposed that chronic cocaine users suffer from a generalized impairment in value processing, likely generalizing to their social lives (11). However, a recent study investigating aging cocaine users with a *Social Incentive Delay Task*, in which the positive feedback is simply given by happy faces and short positive statements, did not find an effect of chronic cocaine exposure on this facet of social reward processing (130). Finally, Hyatt et al. (131) applied an interactive competitive Domino game during fMRI, in order to investigate social reward in current and former cocaine users. Remarkably, only former but not current cocaine users showed altered activation of the dorsal caudate nucleus compared to controls, indicating changes in the reward processing related to social competition. Notably, the VMPFC was included in this region-of-interest-based analysis, thus, these results are difficult to compare with subsequent studies on social reward discussed above.

Entactogenes

Emotion recognition and cognitive empathy

Acute MDMA intake has repeatedly been shown to reduce the identification of negative emotions (132-136), while one study additionally found increased recognition of positive emotions (136). The valence-dependent acute effects of MDMA were found in an emotional face recognition task (132,133) and the RMET (136), whereas cognitive empathy performance measured with the MET was not affected by acute MDMA intake (133,137,138). In contrast to the acute effects, two studies have recently shown that chronic users of MDMA exhibit superior cognitive empathy compared to controls when assessed with complex emotionally laden scenes from the MET (139,140). However, as lower cognitive empathy was clearly correlated with higher MDMA concentrations in hair, one of the author groups concluded that the differences at the group level were likely explained by higher social affiliation motivations of the users, while at higher chronic doses MDMA might nevertheless impair cognitive empathy (140). Moreover, the subjective response to a social exclusion paradigm (Cyberball Game) was not altered in MDMA users (139,141), although unpublished MRI data from our group have suggested increased activation of pain-related circuits such as the ACC during exclusion in MDMA users (141).

Emotional empathy

Wunderli at el (140) and Carlyle et al (139) both showed that chronic MDMA use was not associated with changes of the emotional empathy domain of the MET.

Perspective-taking and ToM

In the MASC, chronic MDMA users displayed better performance than well-matched control individuals, indicating superior mental and emotional perspective-taking in the MDMA users (140).

Social decision-making

Steward et al (142) investigated the acute effects of MDMA on the *Ultimatum Game* in chronic MDMA users, compared to non-intoxicated controls, and found increased cooperative behaviour on the dictator and ultimatum games under the influence of the drug. However, upon the second measurement, 3 days after the MDMA intake, the groups did not differ in any of the social decision-making parameters. In contrast, in the study of Wunderli et al (140), chronic MDMA users (off drug) displayed more prosocial decisions in *Distribution* and *Dictator Games* compared to controls.

Opioids

Emotion recognition and cognitive empathy

Deficits in emotion perception were initially found in detoxified heroin users as well as methadone-maintained heroin users using the picture-based *Emotional Facial Expression Decoding Test* (143). In contrast, in a well-powered study, McDonald et al (144) reported that only methadone- and buprenorphine-maintained heroin-dependent individuals, but not abstinent heroin users without opioid-maintenance therapy, showed generally impaired emotion recognition in the video-based *Awareness of Social Inference Test* (TASIT). Importantly, these group differences disappeared if a general cognitive performance measure was introduced as a covariate in the model, suggesting that deficits in emotion recognition are part of a more general cognitive impairment (144). Using the *Comprehensive Affect Test System* (CATS-A) and the MET, Kroll et al (145) recently demonstrated emotion recognition/cognitive empathy deficits for faces, voices, and complex affective scenes in a group of non-medical prescription opioid users (NMPOU) without a history of heroin use, in which recreational or addicted users were included. Interestingly, a global cognitive empathy score was correlated with morphine equivalent opioid concentrations in hair, indicating a dose-response relationship regarding these deficits. Moreover, in this study performance in executive function tasks was also correlated with cognitive empathy measures in NMPOU; however, accounting for executive function in the statistical model did not change the group differences in cognitive empathy (145). The same study population of NMPOU were also tested for their physiological stress response to social exclusion, with an interesting finding: on the one hand, NMPOU showed hyperreactivity of the endocrinological stress axis and poorer regulation of the parasympathetic nervous system in response to social exclusion, while on the other hand their self-ratings suggested that these users were aware but less emotionally affected by the rejection (146). Taken together, these results suggest that – at least recent or current – opioid use is associated with emotion recognition and cognitive empathy impairments, which co-occurs with – but may not be completely explained by – broader cognitive deficits.

Emotional empathy

Studies in heroin users are thus far lacking, but NMPOU were not impaired in emotional empathy measured with the MET (145).

Perspective-taking and ToM

Again, methadone- and buprenorphine-maintained heroin-dependent individuals, but not abstinent heroin users without opioid-maintenance therapy, showed worse social inference performance in the TASIT, specifically regarding their ability to detect sarcasm. Social inference problems in these patients were also largely explained by their global cognitive impairments (144).

Social decision-making

Hou et al (147) investigated a small sample of heroin-dependent individuals with regard to their decisions in the *Ultimatum Game* and found that, in contrast to healthy controls, heroin users displayed higher rejection rates of most unfair offers under low-offer conditions, while most unfair offers were more likely to be accepted in high-offer conditions. Furthermore, rejection rates of most unfair offers under low-offer conditions were correlated with trait impulsivity measured using the Barratt Impulsiveness Scale. The authors concluded that heroin users acted more impulsively under low-offer conditions, but became more tolerant of inequity specifically in the high-offer condition (147).

Polysubstance use

Emotion recognition and cognitive empathy

Using a computer-based Ekman Faces Test (EFT), deficits in recognition of facial emotion expressions have been reported for substance-dependent individuals with polysubstance use (119,148). Across both of these studies, the effects on fear recognition were largest compared to other emotions. In contrast, a group of mainly recreational polysubstance users did not show any deficits in cognitive empathy (MET) and emotion recognition measures (CATS-A) (120).

Emotional empathy

Recreational polysubstance users showed lower emotional empathy when assessed with the MET and these problems clearly increased with the number of substances used (120). In contrast, only the number of substances, but not single substance classes, such as stimulants, predicted this deficit when introduced in multiple regression models.

Perspective-taking and ToM

In a single study, primarily recreational polysubstance users did not show any abnormalities in the MASC, which measures mental and emotional perspective-taking (120).

Moral decision-making

Two studies have shown that polysubstance-dependent individuals displayed more utilitarian choices when responding to moral dilemmas (92,93).

Discussion

Although the importance of impairments in social cognition and interaction for the development, maintenance and treatment of SUD is self-evident (149), only few studies have yet objectified socio-

cognitive dysfunctions in substance users by means of psychological test paradigms. The only exception to this is emotion recognition in chronic alcohol use, as it has been researched for almost 30 years in a large number of studies, which have provided comprehensive evidence for a generalized emotion recognition deficit in AD that seem to be – at least in part – induced by chronic alcohol exposure. While discussing most of the yet available studies above, it was demonstrated that each substance class is associated with a range of specific impairments in social cognitive functions (see **Table 1** for an overview). However, it was also shown above that there are a number of blank spots on the social cognition and interaction map of substance use that have to be filled in by future studies.

Open Questions

It must be noted that, for most of the substances and functions, the number of available studies is low and, furthermore, most of the studies that have been reported have had rather small sample sizes. Therefore, more studies with larger samples are needed to better characterize the true, specific, socio-cognitive profile of each substance. Although most substance users consume more than only one psychoactive compound, we also currently have only little information about how different substances might interact with each other regarding social cognition. As an example, we have shown detrimental effects of increasing polydrug use on emotional empathy (120), although this study was too small to directly assess specific drug combinations. It must also be noted that protective drug effects are possible, e.g., when considering that MDMA use has been associated with superior socio-cognitive abilities (122). Thus, in samples with mixed stimulant and MDMA use, potential negative effects of stimulants might be compensated by higher socio-cognitive competences of people using MDMA.

Moreover, most of the studies discussed have used relatively passive "first-person" paradigms, such as emotion recognition or ToM tasks, which probably provide only minimal information about the real daily-life social problems users experience in their interactions with other people. Thus, more "second-person" approaches assessing behavioural and neuronal changes in real-life social interactions should be employed, as they are likely more ecologically valid (150). In addition, the relationship between several facets of social cognition (e.g., between emotional empathy and perspective-taking abilities), as well as between social cognition and non-social cognition, needs to be addressed in further studies, as several studies have indicated that socio-cognitive impairments coincide with changes, specifically reductions, in other cognitive functions (26,45,75,76).[1] Nevertheless, it is important to better understand the origin and specificity of socio-cognitive disturbances, especially if targeted socio-cognitive training schemes are to be developed for the improvement of treatment outcomes (see below). Remarkably, it is also not yet fully clear how lifestyle differences, intellectual abilities, and psychiatric comorbidities might influence socio-cognitive deficits in substance users: for example, thus far it has been shown that facial affect recognition deficits of cocaine users might be

[1] Of note, no coherent theory of social cognition or its assumed subcomponents, such as "cognitive empathy" and ToM, has been developed so far, such that different definitions exist and their concepts sometimes overlap (e.g., emotion perception, cognitive empathy, and ToM).

explained by their opioid co-consumption and lower IQ (115), while perspective-taking and cognitive empathy deficits may only appear if a comorbid ADHD diagnosis is present (122,123). Finally, the question also of if (and which) socio-cognitive dysfunctions are predisposed or drug-induced is important for the implementation of new treatments, as acquired impairments are likely to be easier to rehabilitate than predisposed impairments and perhaps "hardwired" dysfunctions. To date, some studies have shown that socio-cognitive problems predict initiation and onset of drug use (101,102), while others clearly showed recovery of such functions with prolonged abstinence (14,15). It has also been proposed that mentalizing deficits in SUD share similarities with such impairments in developmental disorders, such as autism and borderline personality disorder, which argues that such deficits may be rather predisposed (151). The notion that drugs might be instrumentalized by some users to self-medicate social-cognitive deficits has also been suggested (152). However, predispositions to, as well as chronic drug-effects on, social cognition deficits might be substance- as well as function-specific and future longitudinal studies are needed to delineate and characterize these different factors for each substance-using population.

Relevance for treatment

It has been shown that specific impairments in social cognitive functions of substance users are related to real-life social functioning (12,51,79,104,123,130) and that they can be used to predict treatment outcomes (68-70). Although not yet investigated, it is also conceivable that these disturbances of social perception, valuation, and behaviour may directly affect the therapeutic relationship between substance users and their psychiatrist or psychologist and, thus, hamper the success of their addiction treatment. Thus, interpersonal problems affecting all social relationships, including relationships with therapists, might partially explain the high relapse rates after treatment in most SUD (153). Moreover, as social cognition and prosocial behaviour can covary with alterations in substance use across time, indicating their potential for plasticity (14,15), new treatments of SUD might address these specific social problems more distinctively in order to improve the therapeutic relationship and their overall social functional level and, consequently, the treatment success. Promising results in this regard are emerging from other neuropsychiatric disorders, such as traumatic brain injury (154,155), schizophrenia (156-159), autism (160-162), and depression (7) suggesting that socio-cognitive abilities are trainable *per se* and that this can also have a positive impact on treatment outcome. However, social cognitive training schemes specialized for SUD are not available thus far, although recently some encouraging results emerged from very small studies with SUD patients applying mentalization-based interventions – a psychodynamic approach shown to be effective in borderline personality disorder that targets reflective functions such as perspective-taking (163,164). Nevertheless, as is visible in the summary provided in **Table 1**, a single treatment or training approach for all kinds of SUD will not be feasible, as the substance user populations differ in their deficits and, therefore, substance-specific (if not patient-specific) therapy modules have to be developed (165).

Conclusion

When taken together, the research into SUD shows substance-specific profiles of impairments in a variety of socio-cognitive functions and indicates that predisposed or drug-related changes in social reward and social cognition may contribute to the social problems and the decay of social relationships in people with SUD. Beyond that, although not investigated yet, it is likely that disturbances in social perception and behaviour compromise any social interactions, including therapeutic relationships, thus hindering the success of each addiction treatment approach. Accordingly, interpersonal problems related to social cognition deficits might partially account for high relapse rates for those enrolled in any kind of psychological or psychopharmacological treatment developed so far. Additionally, specific social reward deficits might also explain why the social consequences of drug use (e.g., imprisonment or familial problems) do not discourage substance-dependent individuals enough to cease using the drug (12). Therefore, a new focus on psychosocial treatments of stimulant addiction might be needed to address these social dysfunctions in order to improve the therapeutic relationship and treatment success (166). Specifically, the rehabilitation of social reward might be a promising avenue for providing an alternative to bypass the accrual of drug-related reward system maladaptations in SUD (10,12,167).

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Table 1: Changes in performance and behavioural measures of social cognition and interaction in addiction and chronic drug use.

Substance	Emotion recognition and cognitive empathy	Emotional empathy	Perspective-taking and Theory-of-Mind	Social decision-making	Moral decision-making	Social reward
Alcohol	↓	↑,↓,→	↓	↓	↓	?
Cannabis	↓	?(→)	→	?(→)	?	↓
Stimulants	↓,→	↓	↓,→	↓	↓	↓,→
Opioids	↓,→	→	↓,→	↓	?	?
Entactogens	↑	→	→	↑,→	?	?
Polysubstance use	↓,→	↓	→	?	↓	?

↓: finding(s) suggest(s) decrease or impairment, →: finding(s) suggest(s) no change, ↑: finding(s) suggest(s) increase or superiority, ?: not published yet, brackets represent data from so far unpublished pilot studies.

Figure 1: The proposed role of social cognition and interaction in maintenance and relapse of substance use disorders (adapted from: 10).